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ARTICLE

Patient-reported outcomes measures and patient preferences for minimally invasive glaucoma surgical devices

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Abstract

Background Many therapeutic options are available to glaucoma patients. One recent therapeutic option is minimally invasive glaucoma surgical (MIGS) devices. It is unclear how patients view different treatments and which patient-reported outcomes would be most relevant in patients with mild to moderate glaucoma. We developed a questionnaire for patients eligible for MIGS devices and a patient preference study to examine the value patients place on certain outcomes associated with glaucoma and its therapies.

Objectives To summarize the progress to date.

Methods *Questionnaire development:* We drafted the questionnaire items based on input from one physician and four patient focus groups, and a review of the literature. We tested item clarity with six cognitive interviews. These items were further refined. *Patient preference study:* We identified important benefit and risk outcomes qualitatively using semi-structured, one-on-one interviews with patients who were eligible for MIGS devices. We then prioritized these outcomes quantitatively using best-worst scaling methods.

Results *Questionnaire testing*: Three concepts were deemed relevant for the questionnaire: functional limitations, symptoms, and psychosocial factors. We will evaluate the reliability and validity of the 52-item draft questionnaire in an upcoming field test. *Patient preference study:* We identified 13 outcomes that participants perceived as important. Outcomes with the largest relative importance weights were "adequate IOP control" and "drive a car during the day."

Conclusions Patients have the potential to steer clinical research towards outcomes that are important to them. Incorporating patients' perspectives into the MIGS device development and evaluation process may expedite innovation and availability of these devices.

Introduction

Recent innovation in glaucoma procedures has led to the development and application of minimally invasive glaucoma surgical (MIGS) devices. The U.S. Food and Drug Administration (FDA) approved the first MIGS device in June 2012 [1]. FDA in collaboration with the American Glaucoma Society (AGS) held a Workshop on "Supporting Innovation

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for Safe and Effective Minimally Invasive Glaucoma Surgery" in February 2014 [2]. Discussions at the workshop formed a foundation of a leapfrog MIGS Guidance [3]. It was also recognized that evaluation of glaucoma devices had included very little input from patients prior to 2015. Thus, the essential next step for MIGS innovation was incorporation of patient voice.

The past decade, perhaps more than any other period in history, has seen a trend away from the paternalistic approach to healthcare where physicians often decided and conveyed what they thought was best for patients without the patients having a voice in the decision-making process. Health care systems are increasingly incorporating patient-reported outcome measures to ensure that therapeutic and diagnostic approaches are informed by patients' perspectives [4]. Payers are more likely to make favorable coverage decisions for products and procedures that are supported by scientific information obtained from patients. FDA has encouraged and, more recently, issued guidance on patient-reported outcomes and patient preference information to accompany traditional study findings relating to safety and effectiveness endpoints as part of medical device submissions [5, 6]. Patient input can be incorporated into the development, evaluation, and labeling of medical products [6–9].

Health-related quality of life, one type of patient-reported outcome, refers to what patients can do (functioning) and how they feel (well-being) in physical, mental, and social health domains of life [10]. Health-related quality of life domains may include physical functioning, role functioning, social functioning, depressive symptoms, anxiety, anger, positive affect, pain, energy, and general health perceptions. FDA defines patient preference information as "qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions" [6]. Preference information reflects the value that patients place on benefits and risks of therapies. Thus, patients' preferences provide context grounded in information provided by patients to prioritize outcomes. Patient preference information is particularly useful when there are many treatment options available, with none superior for all patients; patients' views about the most important benefits and acceptable risks vary considerably or differ from those of health care professionals; and when the evidence supporting one option over others is uncertain [11].

To facilitate the incorporation of patients' input on glaucoma devices, we formed a consortium of FDA, Centers of Excellence in Regulatory Science and Innovation (CERSIs) at Johns Hopkins University and University of California San Francisco (UCSF)/Stanford, and the AGS. FDA funded the UCSF/Stanford CERSI to develop a patient-reported outcome instrument targeting patient with mild to moderate open angle glaucoma (OAG) eligible for MIGS devices. Concurrently, FDA funded the Johns Hopkins CERSI to conduct a preference study to identify which outcomes matter most to patients with mild to moderate OAG and that affect their risk tolerance and perspective on benefit for MIGS devices. The objective of this paper is to summarize the background and progress on the two projects to date.

Methods

Patient-reported Outcome Instrument Development (Questionnaire)

The first phase of the questionnaire development was a physician focus group conducted in conjunction with the 2016 AGS Annual Meeting. The physician focus group was followed by four patient focus groups conducted at two academic centers (University of California Los Angeles and the University of Pennsylvania) and two private practice groups in Arkansas and Texas. Using the patient eligibility criteria from FDA guidance documents for MIGS device clinical investigations [3], we queried patients with gonioscopy-confirmed mild to moderate OAG about their symptoms, factors important to their quality of life, and how all other aspects of living with glaucoma have impacted their lives.

We used the information from the focus groups and a review of the literature to draft the questionnaire items. We tested the clarity and appropriateness of the items with six cognitive interviews in Arkansas. This draft instrument was subsequently refined iteratively based on input at several live and remote meetings. An AGS Committee chaired by Dr. George Spaeth played a major role in these revisions.

To further refine the questionnaire items, we conducted 19 additional cognitive interviews, five of which were conducted face-to-face in Los Angeles. The other interviews were conducted online using telecommunications applications ($n = 8$) or by phone ($n = 6$). Based upon these cognitive interviews, we refined questions to enhance understanding among those taking the questionnaire.

Patient preferences study

The methods for the patient preference study have been published elsewhere and are summarized briefly below [12, 13]. To explore patients' perspectives and experiences living with glaucoma and to identify important benefits and risks that patients consider before electing treatments such as MIGS devices, we first conducted semi-structured, in-person qualitative interviews with adult patients older than 21 years of age who were suspected or diagnosed with ocular hypertension or mild to moderate OAG seen at the Johns Hopkins Wilmer Eye Institute between May and

December 2016. The interview questions focused on factors patients consider when deciding between different treatments. We used the framework method to code and analyze the qualitative data and focused on considerations expressed by patients that can be translated into outcomes in future MIGS clinical trials [14].

To quantify patients' stated preferences for glaucoma outcomes and use this information to prioritize outcomes that were important to them, we conducted a cross-sectional study using best-worst scaling (BWS) methods based on findings from the qualitative input described above [15]. We recruited adult patients older than 21 years of age who were suspected of or diagnosed with ocular hypertension or mild to moderate OAG from one academic-based and three private glaucoma clinics between September 2017 and February 2018. We administered the survey online and asked participants to rate the importance of outcomes on a 5-point response scale as a warm-up exercise followed by completion of BWS tasks. For each task, we presented participants a subset of outcomes and participants chose the most important and least important outcomes. We analyzed response patterns using conditional logistic regression to determine the relative importance of the different outcomes.

Results

Patient-reported Outcome Instrument Development (Questionnaire)

While most ophthalmologists in the physician focus group were subspecialist members of the AGS, there were also comprehensive ophthalmologists on the panel. The primary specialty was glaucoma ($n = 9$), ophthalmology ($n = 2$), and general/comprehensive ($n = 1$). Ten were men and two were women. Age categories selected by participants were 31–40 years ($n = 1$), 41–50 ($n = 6$), 51–60 ($n = 1$), 61–70 ($n = 2$), and 71 or older ($n = 2$). Table 1 shows the concepts of interest identified by the group.

There were 19 females and 22 males in the patient focus groups: 16 non-Hispanic Whites, 15 African Americans, 7 Hispanics and 3 Asians. Some, but not all these patients had undergone or were candidates for MIGS procedures. Table 2 shows unranked concepts identified in the patient focus groups. Activity limitation, difficulties with night driving, loss of depth perception, esthetic changes, light sensitivity, and reading difficulties were mentioned by both physicians and patients focus groups.

Table 3 provides a summary of the list of concepts deemed relevant for incorporation in the questionnaire empirically divided into three categories: functional limitations, symptoms, and psychosocial factors. Draft items were revised based on the 25 cognitive interviews leading to an increase in the number of items, resulting in a 52-item questionnaire. This questionnaire will be administered in a future field test with 500 or more respondents to evaluate its reliability and validity.

Table 1 Concepts identified by physician focus group

- Activity limitations: climbing stairs, walking, increased falls, difficulty navigating unfamiliar places
- Night driving
- Loss of depth perception
- Esthetics: sunken eye, looking older
- Light sensitivity
- Reading difficulties: decreased reading speeds, difficulty perceiving whole words
- Ocular irritation: dry eyes, foreign body sensation
- Loss of peripheral vision
- Job loss
- Annoyance or anger about having glaucoma
- Worrying about safety and going blind

Underlined text represents categories identified by both physician and patients

Table 2 Concepts identified by patient focus groups

- Activity limitations: tripping and falling when walking, difficulty pouring water into a glass, unable to ski, unable to play basketball, avoiding putting head below heart when exercising
- Night driving: judging distances, peripheral vision
- Loss of depth perception: "smeared vision"
- Esthetics: drooping eye lid, enlarged eye, hyperpigmentation
- Light sensitivity: need to wear sunglasses
- Reading difficulties: needing breaks when reading (or using a computer)
- Double vision from scarring
- Decreased contrast perception: can't see a person's features, losing golf balls
- Difficulty distinguishing colors: dark blue and black, light pink
- Treatment burden: adhering to treatment regimen, nuisance, time consuming, inconvenience, pain, overwhelming
- Drops: drip down throat, cause blurry vision, make one drowsy, cause red/bloodshot eyes

Underlined text represents categories identified by both physician and patients

Patient preference study

Twenty-five patients (10 male and 15 female) with a median age of 69 years (range 47–82) participated in one-on-one interviews [12]. About half (12/25; 48%) were African American; a third (9/25; 36%) were White; and four participants (4/25; 16%) were Asian or another race.

All 25 participants expressed some concerns with their ability to perform vision-dependent activities, such as

reading and driving. All 25 participants also had an opinion about intraocular pressure (IOP), and among those currently taking ocular hypotensive eye drops, all recognized the relationship between eye drops and IOP. We identified 13 outcomes that participants perceived as important across four thematic areas: (1) limitations in performing specific vision-dependent activities of daily living (able to read fine print; drive during the day/at night; and navigate indoors/outside); (2) problems with visual perceptions (able to perceive depth; peripheral vision; and seeing in extreme lighting conditions); (3) treatment burden, including ocular events (reducing number of pressure lowering drops; maintaining appearance of the eye; and not experiencing ocular surface symptoms); and (4) having adequate IOP control. We designed a preference elicitation survey using these 13 outcomes.

Table 3 Areas to target for the questionnaire

• Functional limitations
Climbing stairs, walking, tripping and falling when walking, difficulty pouring water into glass, impairment in sporting activities, needing breaks when reading or using a computer, avoiding driving at night, can't see whole words and slowing of reading speed, can't see a person's features, and difficulty distinguishing colors
• Symptoms
Sensitivity to bright lights, dry, red, bloodshot or irritated eyes, foreign body sensation, "smeared vision," and blurry vision
• Psychosocial factors
Job loss, changes in looks (skin, sunken eye, droopy eyelid, looking older), uncomfortable with unfamiliar places, annoyance or anger about having glaucoma, and worrying about safety and going blind

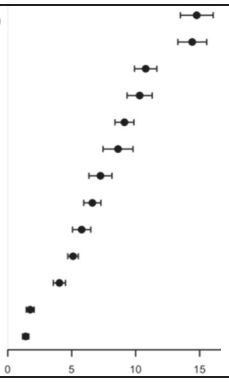
Of 1035 patients we invited to participate in the preference elicitation survey, 274 (26%) responded [13]. More than half of them (146/274, 53%) were older than 65 years of age and were on IOP-lowering drops (179/274, 65%). Most of the participants who responded (196/274; 72%) were White; about 10% (26/274) were African American; and 52 participants (18%) were Asian or another race. Participants identified that outcomes with the largest relative importance weights were "adequate IOP control" and "drive a car during the day," and the outcomes with the smallest relative importance weights were "maintaining appearance of the eye" and "reducing the number of IOP-lowering drops". Table 4 displays the ranking of the 13 outcomes.

Discussion

It is important that outcomes chosen for glaucoma research translate into perceived benefits for glaucoma patients. The next step for evaluating the questionnaire is the field test. It will provide information on the psychometric properties (reliability and validity) of the questionnaire. We are pursuing a partnership with the IRIS® Registry of the American Academy of Ophthalmology (AAO) and Verana Health. Verana Health has an ongoing agreement with the AAO that allows for access to the Registry data. The final questionnaire is expected to be valuable for the advancement of glaucoma care. While developed to assist in device innovation for patients with mild to moderate OAG, it may also prove useful for other research studies as well as clinical applications.

Table 4 Outcomes identified in 25 one-on-one interviews and their relative rankings in preference elicitation survey

Outcome	Relative importance weights (95% CI)		Ratio-scaled weights[a] (95% CI) and Plot		Rank
Have control of intraocular pressure	1.28	(1.09 to 1.47)	14.8%	(13.5% to 16.0%)	1st
Drive a car during the day	1.22	(1.06 to 1.39)	14.4%	(13.3% to 15.5%)	2nd
Maintain mobility outside the home	0.68	(0.55 to 0.82)	10.8%	(9.9% to 11.7%)	3rd
Maintain mobility inside the home	0.61	(0.46 to 0.76)	10.3%	(9.3% to 11.3%)	4th
Perceive depth	0.42	(0.39 to 0.54)	9.1%	(8.4% to 9.9%)	5th
Drive a car at night	0.33	(0.14 to 0.53)	8.6%	(7.5% to 9.8%)	6th
Read fine print	0.09	(–0.08 to 0.26)	7.2%	(6.3% to 8.1%)	7th
See in very dim or very bright light	–0.03	(–0.17 to 0.10)	6.6%	(5.9% to 7.3%)	8th
No ocular surface symptoms	–0.21	(–0.37 to –0.05)	5.8%	(5.1% to 6.5%)	9th
See things off to the side (peripheral vision)	–0.36	(–0.46 to –0.26)	5.1%	(4.7% to 5.5%)	10th
Distinguish color	–0.65	(–0.78 to –0.51)	4.0%	(3.6% to 4.5%)	11th
Reduce number of IOP lowering drops	–1.57	(–1.76 to –1.38)	1.8%	(1.4% to 2.1%)	12th
Maintain appearance of the eye (cosmesis)	–1.81	(–2.00 to –1.62)	1.4%	(1.2% to 1.7%)	13th



CI confidence interval, *IOP* intraocular pressure

*Weights are ratio scaled using a probability-based rescaling procedure: ratio-scaled weight $= e^{Ui}/(e^{Ui} + a - 1)$, where e^{Ui} is the antilog of the zero-centered coefficient for item i and a is the number of items shown per choice set. A preference weight of 10% is twice as preferred as an outcome with a preference weight of 5%

The outcomes identified as important by patients from the patient preference study are congruent with those identified in the questionnaire. A sample of participants across the country prioritized control of IOP and the ability to drive as the most important outcomes. They also expressed that the ability to perform other vision-dependent activities (e.g., navigating inside/outside the house) and maintaining visual perceptions (e.g., depth perception) are more important than burden of treatment (e.g., number of IOP-lowering drops). Many of the outcomes that participants deemed as most important to them are not outcomes that have been measured consistently in MIGS studies [8].

Patients have the potential to steer clinical research activity towards outcomes important to them. Historically, clinical trials are designed to demonstrate efficacy in an experimental context using design features that aim for rapid and clear answers. Surrogate measures and biomarkers are widely used because they are thought to have feasibility advantages. But surrogate measures such as IOP alone are not always in the interest of patients because of concerns about applicability to clinical practice. It is possible that patients have been led by their healthcare providers to place an undue emphasis on IOP control - that IOP is "not of concern to patients until they have been educated, or rather *miseducated*, to believe that there are linear relationships" between eye pressure and what the patient can do or how well they feel [16]. Future studies could explore this hypothesis by recruiting only treatment naïve participants.

Ideally, incorporation of outcomes that capture functioning, well-being, treatment burden, and visual perceptions from patients' point of view are considerations for future MIGS clinical trials. Incorporating the patients' perspectives into the MIGS device development and evaluation process may expedite innovation and availability of these devices and inform patient and healthcare provider decision making on treatments.

Summary

What was known before

- Despite many therapeutic options available for patients with mild to moderate open angle glaucoma, it is unclear how patients view different treatments and which patient-reported outcomes would be most relevant for them.

What this study adds

- Incorporation of outcomes that capture functioning, well-being, treatment burden, and visual perceptions from patients' point of view are considerations for future clinical trials in glaucoma.

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Compliance with ethical standards

Conflict of interest TL, RDH, QNC, and GS have no conflicts of interest to disclose. JTL was a doctoral student at the Johns Hopkins University when this work was conducted. The opinions expressed in this article are the authors' own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government. ME and MET are employees of the U.S. Food and Drug Administration. KS has the following disclosures: Consultant: Alcon, Allergan, Glaukos, Ivantis, Santen, and Sight Sciences.

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